Lymph Node Metastasis From Soft Tissue Sarcoma in Adults

Analysis of Data From a Prospective Database of 1772 Sarcoma Patients

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To examine the natural history of lymph node metastasis from sarcomas and the utility of therapeutic lymphadenectomy, clinical histories of all adult patients identified by a prospective sarcoma database for the 10-year period July 1982 to July 1991 were examined. Of the 1772 sarcoma patients, 46 (2.6%) were identified with lymph node metastasis. Median follow-up of all patients from diagnosis of lymph node metastasis was 12.9 months (range, 0 to 100 months). Median survival for nonsurvivors was 12.7 months (range, 0 to 40.7). The tumor types with the highest incidence of lymph node metastasis are angiosarcoma (5/37 total cases; 13.5%), embryonal rhabdomyosarcoma (ERMS) (12/88 total cases; 13.6%), and epithelioid sarcoma (2/12 total cases; 16.7%). Lymph node metastasis from visceral primary ($p = 0.004$) and malignant fibrous histiocytomas ($p = 0.006$) were associated with particularly poor prognosis. Thirty-one patients underwent radical, therapeutic lymphadenectomy with curative intent, whereas 15 patients had less than curative procedures, in most cases biopsy only. Patients not treated with radical lymphadenectomy had a median survival of 4.3 months (range, 1 to 32) whereas radical lymphadenectomy was associated with a 16.3 month median survival and the only long-term survivors (46% 5-year survival by Kaplan-Meier). The authors conclude that lymph node metastases from sarcoma are rare in adults, but vigilance is warranted, especially in angiosarcoma, ERMS, and epithelioid subtypes. Radical lymphadenectomy is appropriate treatment for isolated metastasis to regional lymph nodes and may provide long-term survival.

Lymph node metastasis is considered an infrequent event in the natural history of soft tissue sarcomas. The rarity of such lymph node metastasis has made the study of their natural history difficult. Most published series are small, retrospective studies, and as individual studies are hard to interpret. Weingrad and Rosenberg in 1978,[1] and Mazeron and Suit in 1987[2] summarized this literature on sarcoma metastasis. In these collected reviews of 47 and 122 studies, respectively, the overall incidence of lymph node metastasis was found to be 9.1% and 10.8% (Table 1). Even though these data suffer both from being retrospective data and from being collected data from a heterogeneity of therapeutic approaches, they lend support to two clinical impressions concerning lymphatic spread and sarcomas: that they are rare, and that lymphatic spread is more frequently associated with certain histologic types.

It is generally agreed that because of the rarity of such metastases, elective lymphadenectomy for sarcoma is generally not indicated.[1,3] There is less agreement as to

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Table 1. HISTOLOGIC TYPE OF SARCOMAS AND LYMPH NODE METASTASIS

Histologic Findings	No. of Nodal Metastases/All Sarcoma Patients			% of All Lesions		
	Weingrad*	Mazeron†	Current Study‡	Weingrad	Mazeron	Current Study
Fibrosarcoma	55/1083	54/215	0/162	5.1	4.4	0
Malignant fibrous histiocytoma	1/30	84/823	8/316	3.3	10.2	2.6
Undifferentiated spindle cell	—	—	0/42	—	0	—
Rhabdomyosarcoma	108/888	201/1354	1/35	12.2	14.8	2.9
Embryonal rhabdomyosarcoma	—	—	12/88	—	—	13.6
Leiomyosarcoma	10/94	21/524	9/328	10.6	4.0	2.7
Neurofibrosarcoma/MPNT	0/60	3/476	2/96	0	0.6	2.1
Vascular	—	43/376	—	—	11.4	—
Angiosarcoma	NI	—	5/37	45.0	—	13.5
Hemangiopericytoma	3/23	—	0/21	13.0	—	0
Lymphangiosarcoma	—	—	1/4	—	—	25.0
Osteosarcoma	20/327	—	0/11	6.1	—	0
Chondrosarcoma	—	—	1/46	—	—	2.2
Synovial sarcoma	91/535	117/851	2/145	19.1	13.7	1.4
Epithelioid sarcoma	—	14/70	2/12	—	20	16.7
Liposarcoma	15/288	16/504	3/403	5.7	3.2	0.7
Alveolar soft part sarcoma	6/62	3/24	0/13	9.7	12.5	0
Clear cell sarcoma	—	11/40	—	—	27.5	—
Other	11/125	—	0/27	8.8	—	0
Total	320/3515	567/5257	47/1772	9.1	10.8	2.6

Review of past studies of nodal metastasis from sarcomas and current study.
* Adapted from a review by Weingrad and Rosenberg,[1] summary of 47 studies.
† Adapted from a review by Mazeron and Suit,[2] summary of 122 studies.
‡ Database only includes extraskeletal osteo- and chondrosarcomas.
MPNT, malignant peripheral nerve tumor; NI, not indicated.

the prognosis and treatment of clinically evident lymph node metastasis. Some investigators consider lymph node metastasis an indication of disseminated disease,[1,4] and any treatment of these lymph nodes only palliative,[4] whereas others believe an aggressive approach of treatment can bring about long-term survivors.[2] To date, there are only nine studies,[2-9] with a cumulative total 115 patients, that present details of follow-up after treatment of nodal metastasis from sarcomas in adults. Furthermore, most of the details presented are sketchy. In the current study, we examined the incidence and natural history of lymph node metastasis in patients from a large prospective database.

MATERIALS AND METHODS

All adult patients (>16 years of age) admitted to the Memorial Sloan-Kettering Cancer Center (MSKCC) with the diagnosis of sarcoma in the 10 year period from July 1982 to July 1991 were identified in the Department of Surgery Prospective Sarcoma database. From this database of 1772 patients, 46 were identified with lymph node metastasis. Data for these patients with lymph node metastasis then were extracted from the database, hospital and office charts, as well as interviews with patients. Histologic evidence of metastasis was reviewed by the pathology department of MSKCC.

Data examined included: (1) demographics (including age, sex); (2) pathology of primary, recurrences, and metastasis; (3) clinical course of primary, recurrent, and metastatic disease; (4) characteristics of lymph node metastasis (regional *vs.* nonregional metastasis; isolated *vs.* disseminated metastasis); (5) surgical and adjuvant treatment of primary and metastasis; and (6) outcome. Follow-up was by personal contact with the patient, patients' family, or attending physician.

Survival was calculated according to the methods of Kaplan and Meier.[10] The log-rank test was used to compare differences in survival distributions observed in subsets of patients.[10] Survival end points are based on survival after primary disease as well as survival after lymph node metastasis.

RESULTS

Demographics

Forty-six patients were identified with lymph node metastasis from their sarcomas. Average age of the pa-

tients was 48.0 years (range, 16 to 87 years). Twenty-four of the 46 patients were male. Median follow-up from primary diagnosis was 31.1 months (mean, 41.9 months; range, 0 to 23 years). Median follow-up from diagnosis of lymph node metastasis was 12.9 months (mean, 21.7 months; range, 0 to 100 months). Median survival from diagnosis of lymph node metastasis for the nonsurvivors was 12.7 months (mean, 14.4 months; range, 0 to 40.7 months).

Pathology

The overall prevalence of lymph node metastasis was 2.6% of the total. The histologic tissue types of the sarcomas associated with lymph node metastasis are listed in Table 1. The tumor types with the highest prevalence of lymph node metastasis are angiosarcoma (5/37 total cases; 13.5%), embryonal rhabdomyosarcoma (12/88 total cases; 13.6%), and epithelioid sarcoma (2/12 total cases; 16.7%). There were eight cases each of lymph node metastasis from leiomyosarcoma and malignant fibrous histiocytoma (MFH), but because of the high prevalence of each of these tumor types, these metastatic lesions represented only 2.5% and 2.6%, respectively, of the total. No conclusions can be drawn concerning osteosarcoma from the current study, because only cases of extraskeletal osteosarcoma are included in the current database.

Forty-five of the 46 patients had high-grade sarcomas. The one low-grade sarcoma in this series was that in a 52-year-old woman with a chondrosarcoma of the proximal thigh. Sixty-three months after a wide local excision, she had local recurrence and pelvic lymphadenopathy, prompting a hemipelvectomy for pathologically proven local disease and three iliac nodes positive for metastatic disease.

Natural History

Sites of the primaries associated with lymph node metastasis are shown in Table 2. The distributions of primary lesions associated with lymph node metastasis are not dissimilar to the distribution of primaries for all patients in the database. Twenty-one patients presented with a lymph node metastasis at the time of the diagnosis of the primary. The mean time from diagnosis of primary to discovery of lymph node metastasis was 20.1 months (range, 0 to 177 months). Thirty-five of the lymph node metastasis were considered isolated metastasis at the time of their discovery. Of these, 19 went on to have further local or distant metastasis after treatment of the lymph node metastasis, with a mean time to further recurrence of disease of 15.8 months (range, 1 to 59 months).

Table 2. LYMPH NODE METASTASIS FROM SARCOMAS ACCORDING TO SITE OF PRIMARY

Site	No. (%)	% in Database
Head and neck	5 (10.9)	4.8
Upper extremity	7 (15.2)	15.3
Lower extremity	19 (41.3)	38.3
Trunk	5 (10.9)	9.0
Other	7 (15.2)	14.5
Visceral	3 (6.5)	12.7
Thoracic	0 (0)	5.4
Total	46	

%, percentage of sarcomas at each anatomic site associated with lymph node metastasis; % in database, percentage of sarcomas in the entire database at each anatomic site.

Treatment of Lymph Nodes

Thirty-one of the 46 patients had what was thought to be curative surgical procedures in the form of radical lymphadenectomies for isolated regional metastasis. The remaining had noncurative procedures, including biopsy, excision, and limited lymphadenectomy for local toilet. Of note, four of the patients who were thought to have clinically isolated regional lymph node metastasis had only excisional biopsies as surgical therapy. One of these was additionally treated with external beam radiation for a neck metastasis from a scalp angiosarcoma. This patient died of widely metastatic disease 31 months after the radiation therapy. The other three patients who had only biopsies for isolated lymph node metastasis included an inguinal metastasis from a thigh MFH, an axillary metastasis from a hand embryonal rhabdomyosarcoma, and a supraclavicular metastasis from a trunk leiomyosarcoma. All three died within 5 months of the discovery of the lymph node metastasis.

Survival

Overall median survival for these 46 patients calculated from time of primary lesion is 30.0 months and calculated from time of nodal metastasis is 12.8 months (Fig. 1). By univariate analysis, three factors portent particularly poor prognosis (Table 3). These are visceral location of primary, histologic type of MFH, and limited surgery for lymph node metastasis.

Three visceral primaries were associated with lymph node metastasis. These included one from an angiosarcoma of the ileum to para-aortic lymph nodes, an esophageal leiomyosarcoma to para-esophageal lymph nodes, and a leiomyosarcoma of the bladder to pelvic lymph

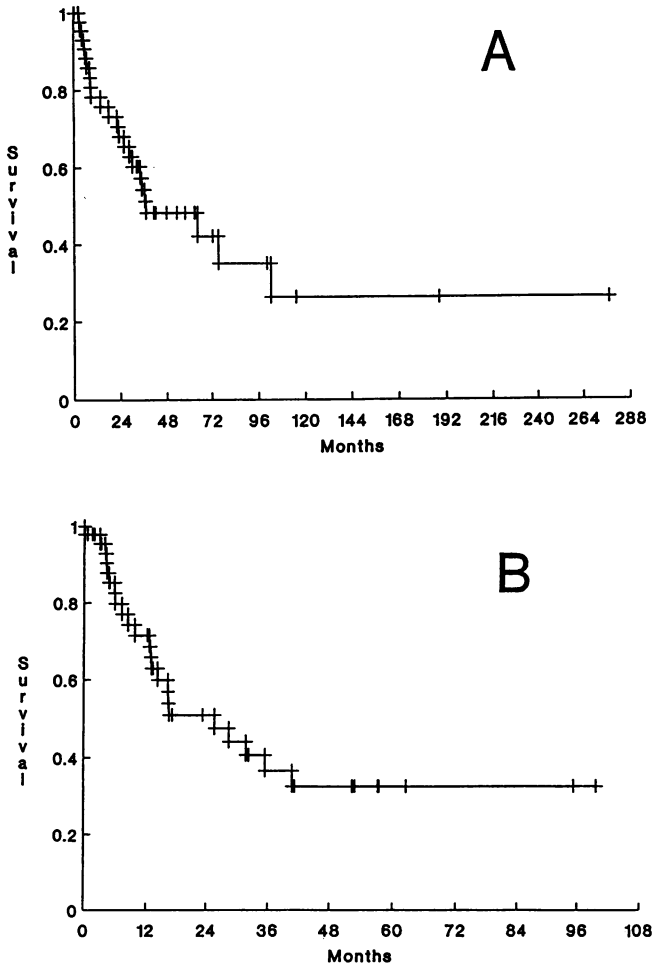

Figure 1. Overall estimated survival for patients with lymph node metastasis from sarcomas. (A, top) Survival calculated from time of treatment of primary sarcoma lesions. (B, bottom) Survival calculated from time of treatment of nodal metastasis (n = 46).

nodes. All patients with visceral primaries were dead of their disease within 10 months of the lymph node metastasis.

Eight patients with lymph node metastasis had the histologic type MFH. The median survival for these patients was 12.7 months (range, 0.7 to 16.3 months) (Fig. 2). All were dead of their disease except for one patient who was only 0.7 months after resection of his groin lymph node metastasis at the time of this report.

Patients not treated with radical lymphadenectomy had a median survival of 5.9 months (range, 1 to 31) whereas radical lymphadenectomy was associated with a 16.3-month median survival, and the only long-term survivors (46% 5-year survival by Kaplan-Meier) (Fig. 3). Profiles of the nine patients with survival greater than 36 months after nodal metastasis are presented in Table 4. One died of other causes 57 months after resection of nodal disease and was without clinical recurrence at the time of death. Seven others are without clinical disease at the time of this report.

Table 3. FACTORS THAT ADVERSELY INFLUENCED SURVIVAL AFTER LYMPH NODE METASTASIS FROM SARCOMA

Factor	No.	p
Age < 30 yr	11/46	0.19
Male sex	24/46	0.55
Lymph node metastasis at time of primary	21/46	0.79
Nonextremity lesion	20/46	0.93
Visceral lesion	3/46	0.004*
Embryonal rhabdomyosarcoma	12/46	0.84
Malignant fibrous histiocytoma	8/46	0.006*
Noncurative surgery	15/46	0.003*

* $p < 0.05$.

DISCUSSION

The overall prevalence of 2.7% for nodal metastasis from sarcomas found in the current study is one-fourth that estimated by prior collected reviews.[1,2] It is not surprising, however, that the prevalence of nodal metastasis from all sarcomas as well as from most individual histologic types determined in the current study (Table 1) is considerably lower than that in prior retrospective studies. One major flaw of retrospective studies is the difficulties in determining the total number of patients at risk. Therefore, these studies often overestimate the incidence and prevalence of disease conditions. Our current results, however, agree well with the prevalence of nodal

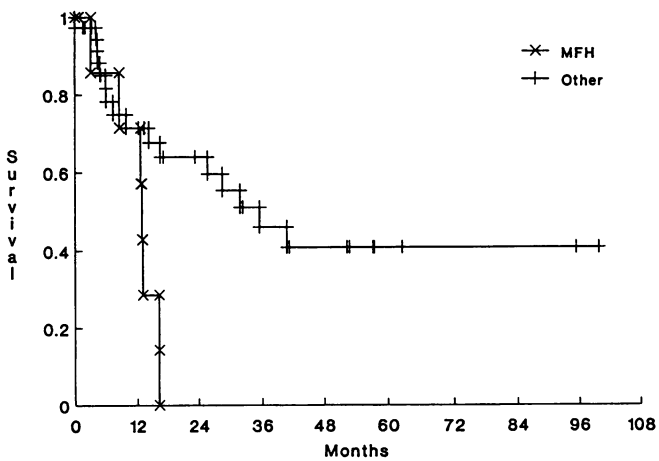

Figure 2. Estimated survival after nodal metastasis for patients with histologic diagnosis of MFH (n = 8) compared with other histologic types of sarcomas (n = 38, p = 0.0064).

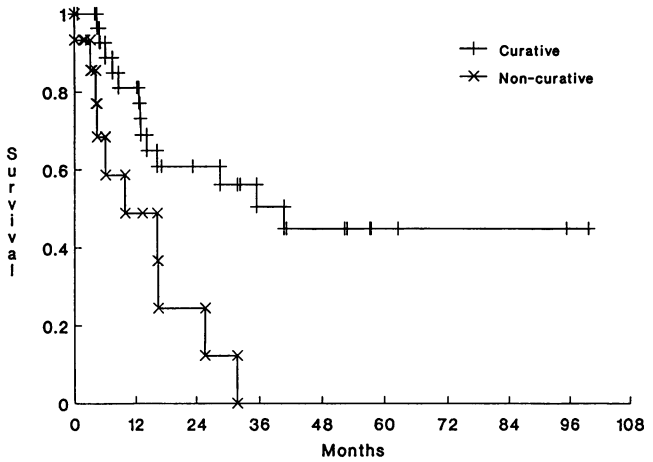

Figure 3. Estimated survival after nodal metastasis for patients treated with radical lymphadenectomies (curative) (n = 31) compared with non-curative surgery (non-cur) (n = 15, p = 0.0027).

metastasis estimated by the study of Weingrad and Rosenberg.[1] In that study, they reviewed data for 113 patients who underwent a major amputation for sarcoma where regional lymph nodes were included within the specimens. Nodal metastasis was found in three of these specimens for a prevalence of nodal metastasis of 2.6%.[1] Certainly, the clinical impression that elective lymphadenectomy is not warranted for soft tissue sarcomas is supported by the low prevalence of nodal metastasis found in the current results.

The current data also would confirm previous findings that the histologic subtypes of angiosarcoma,[1,2,11,12] and epithelioid sarcoma[1,2,8,13] are particularly prone to nodal metastasis. Previous reports had also indicated a high incidence of nodal metastasis for rhabdomyosarcomas,[1,2] particularly in the pediatric age group.[14] The current report finds that in the adult patient population, only the embryonal variant of rhabdomyosarcomas had a particularly high prevalence of nodal metastasis. This prevalence was found to be 13.6% (Table 1). The prevalence of nodal metastasis for the other variants of rhabdomyosarcoma, however, was only 2.9%. The current study also fails to confirm previous reports of high rates of nodal metastasis from synovial[9,15,16] or alveolar soft part[17,18] sarcomas.

Even though two factors appeared to be associated with particularly poor prognosis, namely, histology of MFH and lack of curative resection, great caution must be used in determining clinical utility of such findings. We do not suggest that surgical resection for nodal metastasis from MFH should not be performed, because superior, alternative therapy is not available. Additionally, no definitive conclusion that curative surgical resection was the major determinant of improved outcome can be drawn from the current study, because 12 of the 16 patients in the comparison group, the noncurative surgery group, had unresectable disease. As demonstrated by the current report, however, even in a major referral center for sarcomas, only 35 patients with potentially curable lymph node metastasis over a 10-year period were seen. No meaningful randomized study examining the efficacy of radical resection for such nodal metastasis could be performed in a reasonable period, even if ethical objections to such a study because of a lack of an effective, alternative treatment can be overcome. The data are clear, however, that radical surgery with curative intent is associated with long-term survivors and in the current study the only long-term survivors (Table 4).

In conclusion, lymph node metastases from sarcoma are rare, but vigilance is warranted, especially in angiosarcoma, embryonal rhabdomyosarcoma, and epitheli-

Table 4. PROFILES OF PATIENTS WHO SURVIVED MORE THAN 36 MONTHS AFTER RESECTION OF NODAL METASTASIS

Age	Sex	Pathologic Findings	Site		Treatment of Nodal Metastases	Survival* (mos) (primary/nodal)	Status
			Primary	Nodal			
46	F	Lymphangiosarcoma	Leg	Inguinal	Hemipelvectomy	115.2/57.4	DOC
36	F	Synovial	Chest	Axillary	Axillary dissection/chemotherapy	62.8/62.6	NED
62	F	Leiomyosarcoma	Leg	Inguinal	Inguinal dissection	276.9/99.6	NED
29	M	ERMS	Perineal	Inguinal	Inguinal dissection/chemotherapy	100.3/95.3	NED
18	M	ERMS	Testicular	Retroperitoneal	Retroperitoneal dissection/chemotherapy	57.6/57.1	NED
73	F	Leiomyosarcoma	Thigh	Inguinal	Inguinal dissection	75.4/40.7	DOD
59	M	Liposarcoma	Leg	Inguinal	Inguinal dissection	62.5/52.3	NED
66	F	Leiomyosarcoma	Retroperitoneal	Retroperitoneal	Para-aortic dissection/chemotherapy	53.2/52.8	NED
41	M	Leiomyosarcoma	Thigh	Inguinal	Inguinal dissection	41.2/41.2	NED

* Calculated from diagnosis of primary (primary) as well as calculated from time of diagnosis of nodal metastasis (nodal). ERMS, embryonal rhabdomyosarcoma. DOC, dead of other causes/patient had no clinically apparent recurrence at the time of death; NED, no evidence of disease; DOD, dead of disease.

oid subtypes. With an overall 5-year survival after nodal metastasis of 34% by Kaplan-Meier (Fig. 1), prognosis of such metastasis is poor, but certainly not hopeless. Radical lymphadenectomy is appropriate treatment for isolated metastasis to regional lymph nodes and may provide long-term survival.

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